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Collateral damage of the COVID-19 pandemic on lysosomal storage diseases: A single unit experience

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Abstract
Aim: COVID-19 epidemic caused significant problems in countries' health systems. The direct and indirect effects of this unprecedented outbreak on patients with rare diseases are not clear. The aim of this study is to identify the pandemic-related problems encountered by adults with LSDs and parents who have children with LSDs and to evaluate the socio-economic and psychological effects of the COVID-19 outbreak in the lysosomal diseases community.
Material and Methods: Our study included 27 adult patients receiving ERT treatment and 19 parents of child patients who were followed up with LSD diagnosis. Sociodemographic Data Form and COVID-19 Traumatic Stress Scale were applied to patients and their parents.
Results: We found that treatment was disrupted in 44.4% of adult patients and 36.84% of child patients due to the COVID-19 outbreak. We found that 50% of adults and 80% of parents had a fear of going to the hospital due to the COVID-19 pandemic. Economic distress was higher in the treatment-disrupted group. Also, patients who had a fear when going to the hospital for ERT had higher "fear/threat of infection" scores.
Discussion: The pandemic brought wide-ranging changes in the treatment and follow-up of patients with rare diseases. Home therapy appears to be the most effective way to maintain access to treatment during a pandemic; however, the personnel involved should be monitored and much attention should be paid to the proper use of personal protective equipment. It is also of great importance to provide adequate social, economic and psychological support to individuals.

Keywords
COVID-19 Pandemic, ERT, Lysosomal Storage Disease, COVID-19 Traumatic Stress Scale

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Introduction

The coronavirus disease-19 (COVID-19) epidemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global problem that has affected the entire world since March 2020. Concerns about infection, loss of income/employment, disruption of routines, physical isolation from friends and family, restriction of leisure activities and closure of schools and nurseries have created significant stress for patients and clinicians. The COVID-19 epidemic has caused significant problems in countries' health systems and countries faced with an unprecedented health crisis [1]. Countries' health systems have been overloaded by the burden of the pandemic due to the increase in the number of cases and the lack of a specific and effective treatment. The COVID-19 outbreak has caused growing concern around the world due to the fear of infection, especially in people with chronic diseases [2].

The direct and indirect effects of this unprecedented outbreak on patients with rare diseases are still not clear. People with rare metabolic disorders are at risk during a pandemic due to multisystemic involvement, including vital organs [3]. In particular, patients with lysosomal storage disease (LSD) are considered to be at high risk of severe COVID-19 infection, as they often suffer from a multisystemic disease that also includes respiratory and cardiovascular system involvement [4]. It is well known that SARS-CoV-2 uses the lysosomal system to infect cells [5]. Therefore, those with lysosomal storage disease may be considered at increased risk for COVID-19 infection and complications due to lysosomal dysfunction and activation of inflammatory cascades [6].

Lysosomal storage diseases are rare, inherited group of metabolic disorders characterized by the progressive accumulation of undigested substrates within the lysosome. Currently, many LSD's, such as Gaucher, Fabry, Pompe diseases, can be treated with enzyme replacement therapy (ERT) [7]. Although many countries offer infusions at home, in Turkey, patients must go to hospitals every 1 or 2 weeks to receive treatment. Although treatments such as hematopoietic stem cell transplantation and substrate reduction therapy are available for a limited number of LSD's, ERT is currently the only approved and the most effective treatment for most [8]. In a limited number of studies, it was noted that during the pandemic process, patients who received regular ERT prior to it disrupted their infusions [2, 9-11].

The risk of infection in a pandemic increases fear and stress in societies. Despite a large number of studies that have been conducted on the global epidemic, the number of studies on COVID-19 anxiety is limited. It is important to identify the problems faced by patients with rare metabolic diseases during the pandemic, as well as their attitudes towards ERT to ensure the sustainability of their treatment. To the best of our knowledge, the association of the COVID-19 pandemic with LSDs, which has previously been investigated in limited and non-face-to-face studies and mostly in the pediatric population, was not investigated in the adult patient group. The aim of this study is to identify pandemic-related problems encountered by adults with LSDs and parents who have children with LSD and to evaluate the socio-economic and psychological effects of the COVID-19 outbreak in the lysosomal diseases community, as well as health service and treatment disruptions. Also, we aimed to enrich the literature by investigating the traumatic effects of the COVID-19 pandemic using a structured traumatic scale.

Material and Methods

Study sample

The study included 27 adult patients receiving ERT treatment and 19 parents of child patients who were followed up with LSD diagnosis at XXX University Faculty of Medicine Department of Pediatric Metabolism.

Procedure

Adults and parents of children with LSD who were followed up by XXX Faculty of Medicine, Department of Pediatric Metabolism were reached via telephone and e-mail. The research related to human use complied with all the relevant national regulations, institutional policies, and in accordance with the tenets of the Helsinki Declaration, and ethics committee approval was obtained from XXX Ethics Committee, with a decision number 497, dated 09.03.2021. All patients and parents of patients have signed informed consent. The data were collected between March and May 2021. Participants' compliance with ERT treatment during the COVID-19 pandemic was evaluated from hospital records.

Tools

The socio-demographic Data Form and COVID-19 Traumatic Stress Scale were applied to patients and their relatives. The application tools were applied face-to-face to the 16 adults and 14 parents who were continuing the ERT treatment, while the remaining 11 adults and five parents were reached online.

Socio-demographic Data Form: It is a 26-question data form created by researchers. It consists of three parts: the first part contains the socio-demographic data of the participants such as age, gender. The second part contains information about LSD and ERT treatments and the third part contains data on participants' daily routine changes due to the COVID-19 pandemic. Problems encountered during hospitalization or access to medications for ERT were identified by evaluating hospital records.

COVID-19 Traumatic Stress Scale: A 12-point Likert-type scale was developed by Kira et al. in 2020 [12]. The COVID-19 Traumatic Stress Scale consists of three dimensions: "fear/threat of infection and death", "economic distress", and "disrupted routine/isolation". The validity and reliability of the scale in Turkish was conducted by Altınöz et al [13].

Statistical Analyses

Continuous data were given as mean ± standard deviation. Categorical data were given as percentages (%). The Shapiro–Wilk test was used to investigate the suitability of the data for normal distribution. To compare the non-normally distributed groups, we used the Mann–Whitney U test for the data with two groups. IBM SPSS Statistics 21.0 was used for the analyses. A p-value of < 0.05 was considered statistically significant.

Results

Twenty-seven adults with LSD and 19 parents of children with LSD participated in the study. The mean age was 37.33±10.82 years (20-68). Among them, 27 (57.8%) were women and 19 (41.3%) were men. Regarding the most striking findings, we

Table 1. Sociodemographic characteristics of participants

		Patient (n=27)	Parent (n=17)
Age (Year), Mean±SD, (Min-Max)		36.04±12.54 (20-68)	39.65±8.05 (21-50)
Gender, n(%)	Woman	16 (53.9%)	11 (64.7%)
	Man	11 (40.7%)	6 (35.3%)
Marital status n(%)	Married	16 (53.9%)	15 (88.2%)
	Single	11 (40.7%)	2 (11.8%)
Employment status n(%)	Working	13 (48.1%)	8(47.1%)
	Not working	14 (51.9)	9 (52.9)
Perceived income level n(%)	Low	10 (37%)	8(47.1%)
	Middle	16 (59.3%)	9 (52.9)
	High	1 (3.7%)	-
Having a child n(%)	No	14 (51.9%)	-
	Yes	13 (48.1%)	17 (100%)
History of a psychiatric disorder	Yes	1 (3.7%)	-
	No	26 (96.3%)	17 (100%)
Smoking	Yes	6 (22.2%)	6 (35.3%)
	No	21 (77.8%)	11 (64.7%)
Alcohol use	Yes	5 (18.5%)	1 (5.9%)
	No	22 (81.5%)	16 (94.1%)

Table 2. Disease and treatment characteristics in the patient group

	Adult Patient (n=27)	Child Patient (n=19)
Diagnosis, n(%)		
Gaucher Type 1	16 (59.3%)	3 (15.78%)
Gaucher Type 3	-	3 (15.78%)
Fabry	6 (22.2%)	1 (5.26%)
Pompe	1 (3.7%)	1 (5.26%)
MPS Type 1	-	1 (5.26%)
MPS Type 2	1 (3.7%)	2 (10.52)
MPS Type 4A	2 (7.4%)	4 (21.05%)
MPS Type 6	1 (3.7%)	4 (21.05%)
ERT Duration (Month) Mean±SD (Min-Max)	75.48±62.29 (24-240)	57.28±44.23 (3-132)
ERT Treatment, n(%)		
Imiglucerase	12 (44.4%)	6 (31.57%)
Taliglucerase alpha	4 (14.8%)	-
Idursulfase	1 (3.7%)	-
Idursulfase beta	-	2 (10.52%)
Elosulfase Alpha	2 (7.4%)	4 (21.05%)
Galsulfase	1 (3.7%)	4 (21.05%)
Agalsidase beta	3 (11.1%)	1 (5.26%)
Agalsidase Alpha	3 (11.1%)	-
Alglucosidase Alpha	1 (3.7%)	1 (5.26%)
Laronidase	-	1 (5.26%)
ERT protocol		
Once in a week	4 (14.8%)	11 (57.9%)
Biweekly	23 (85.2%)	8 (42.1%)
ERT treatment disruption		
Yes	12 (44.4%)	7 (36.84%)
No	15 (55.6%)	12 (63.16%)
Reason for the disruption		
Fear of going to the hospital due to COVID-19	7 (50%)	4 (80%)
Fear of the public transportation due to COVID-19	0	0
Treatment is not available-disrupted in the hospital	0	0
Having a COVID-19 infection	7 (50%)	1 (20%)

Table 3. COVID-19 characteristics of participants

		Patient (n=27)	Parent (n=19)
History of a COVID-19 infection, n(%)	Yes	7 (25.9%)	2 (10.5%)
	No	20 (74.1%)	17 (89.5%)
Someone diagnosed with COVID-19 in the same house	Yes	0 (0%)	2 (10.5%)
	No	27 (100%)	17 (89.5%)
COVID-19 diagnosis in a first degree relative	Yes	9 (33.3%)	4 (21.1%)
	No	18 (66.7%)	15 (78.9%)
Death from COVID-19 in the same house	Yes	-	2 (10.5%)
	No	27 (100%)	17 (89.5%)
Death of a first degree relative due to COVID-19	Yes	1 (3.7%)	-
	No	26 (96.3%)	19 (100%)
Compliance with restrictions in the COVID-19 pandemic	Yes	27 (100%)	19 (100%)
	No	-	-
Concern over COVID-19 outbreak while having ERT in the hospital	Yes	22 (81.5%)	13 (68.4%)
	No	5 (18.5%)	6 (31.6%)
Concern over COVID-19 outbreak on the way to hospital for ERT	Yes	19 (70.4%)	10 (52.6%)
	No	8 (29.6%)	9 (47.4%)
Concern over COVID-19 outbreak on the way to pharmacy for drug supply	Yes	15 (55.6%)	11 (57.9%)
	No	12 (44.4%)	8 (42.1%)
Would you consider getting ERT at home	Yes	26 (96.3%)	17 (89.5%)
	No	1 (3.7%)	2 (10.5%)

observed that most of the adult patients had Gaucher Type 1 (59.3%), and most of the children had mucopolysaccharidosis group diseases. We found that 44.4% (N=12) of adult patients and 36.84% (n=7) of children patients' treatment were disrupted due to the COVID-19 outbreak. When the reasons of the disruptions were examined, we found that %50 of adult patients (n=7) and %80 of parents had a fear of going to the hospital due to the COVID-19 pandemic. Also, we found that 50% of adult LSD patients (n=7) and 20% of parents (n=1) were diagnosed with COVID-19, thus they discontinued the ERT treatment. We also found that 7.9% of patients received ERT treatment at home. Socio-demographic data of the participants are summarized in Table 1, the data regarding lysosomal disease are summarized in Table 2, and the characteristics associated with COVID-19 are summarized in Table 3.

We found that all of the LSD patients and their parents complied with the restrictions in the COVID-19 pandemic. When patient and parent groups were evaluated in terms of COVID-19 traumatic stress scale scores, there was no statistically significant difference found in fear/threat of infection, economic distress and disrupted routine/isolation ($p>0.05$). In the LSD patient group, a significant difference was found between patients whose treatments were disrupted due to COVID-19 and who continued the treatment as usual, in terms of "economic distress" scores ($p=0.048$). Also, patients who had a fear when going to the hospital for ERT scored significantly higher in COVID-19 traumatic stress scale in "fear/threat of infection" sub-dimension ($p=0.019$).

Discussion

Undesirable conditions associated with COVID-19 significantly affected the access of people with chronic diseases to health care [1]. This group of diseases affects a vulnerable population, not only because of the effects of the disease itself, but also

because they are dependent on proper health care. As most hospitals focus on the treatment of patients severely affected by COVID-19, several problems aroused in the treatment and follow-up of patients with chronic diseases. In addition, the risk of contracting COVID-19 disease increases due to the fact that these patients have to go to medical facilities [10].

One of the most important findings of our study is that the rate of COVID-19 infection in adult LSD patients was 25.9% (n=7) and 10.5% (n=2) in parents. This rate is significantly higher than the total COVID-19 patient rate in Turkey, which is 6.06%, as of May 2021. Although our study sample fully complied with the restriction rules, this rate is significantly higher than that of the general population. This may be associated with the need for frequent admission to hospitals and increased exposure to COVID-19. In these individuals at high risk for COVID-19 infection due to lysosomal dysfunction and inflammatory sensitivity, home treatment options are of high importance to ensure the continuity of LSD treatment, the reduction of COVID-19-induced anxiety and the reduction of COVID-19-associated morbidity and mortality [6-8]. Having the freedom to choose the date and time for the infusion, the opportunity to maintain functionality and to plan daily activities in a much more comfortable and private environment for the patient increases compliance with the treatment and the quality of life. Brunelli et al. conducted a cross-descriptive study to evaluate the advantages and the disadvantages of a home care program for patients with LSDs [14]. In the patient group, 86.9% chose to continue the treatment at home, and 88.5% felt that their quality of life has improved. The authors reported the main benefits of home treatment are higher adherence to treatment and improved quality of life [14]. The possibility of avoiding going to the health center in special situations such as pandemics, the opportunity to reduce the risk of infection that may occur in the hospital are important advantages and should be taken into consideration when treating these vulnerable groups in pandemics.

Regarding the studies related to the treatment of patients with LSD during the COVID-19 pandemic process, Sechi et al. found that 49% of adult LSD patients receiving hospital treatment had a disruption in treatment [11], whereas Kahraman et al. found that this rate is 46.7% [9]. In our study, the similar rates of those who had a disruption in the treatment indicate that approximately half of the LSD patients have COVID-19-related disruptions in their treatment, even though they live in different regions in the world. Disruption in treatment increases morbidity and mortality rates in these individuals, also it can lead to the progression of the underlying disease and cause irreversible outcomes [10]. In the study by Drelichman et al., it was reported that splenomegaly, hepatomegaly and bone-related complications could be seen in individuals with LSD as a result of suspending ERT for more than 2 months, and it is stated that these complications may be irreversible [15]. Since there is no home treatment option available in Turkey today, 93.5% of all patients in our study cannot access it, even if they want to. Considering the possible adverse effects of treatment disruption, it seems to be important to identify individuals who have difficulty accessing treatment and to present alternative treatment options.

Considering the causes of treatment disruptions, we found that the most common reason for the treatment disruption was fear of going to the hospital (59.2%). Similarly, Kahraman et al. also found that the most common reason for the treatment disruption was "being afraid to go to the hospital" (74.3%) [9], and Sechi et al. found that 62.9% of patients whose treatments were disrupted had a fear of getting an infection [11]. In a study by Fiumara et al., they found that pediatric LSD patients had an increase in their COVID-19 related anxiety, and 60% of them had a treatment disruption, due to the fear of COVID-19 infection [2]. In our study, the fact that both the patient group and parents received similar scores in all sub-dimensions in the traumatic scale, especially the fear of infection and fear of death/threat sub-dimensions, shows that COVID-19 affects all groups in similar ways in sense of anxiety and social problems. Our findings show that patients who were continuing their treatments regularly also had higher anxiety levels, and that these levels increased the most while receiving treatment in the hospital. Similarly, Fiumara et al. also found that people who were treated regularly with ERT had a high level of anxiety about getting COVID-19 [2]. This indicates that the problem experienced by individuals with LSD is not only treatment disruptions and complications they have thereafter, it also shows that they are going on with their lives under a high anxiety burden. Although alternative treatment options may reduce these patients' anxiety levels, psychological interventions may also help their anxiety and improve their quality of life.

Regarding the COVID-19 traumatic scale, we also found that the economic distress sub-dimension score was statistically significantly higher in the disrupted group. These data shows that the causes, which are disrupting the LSD treatment are not only related to disease anxiety and can be multi-factorial. Since the vast majority of the patients in our study are of low-to-middle income and about half of them are unemployed, these people may be even more affected by the additional economic difficulties caused by the COVID-19 pandemic. According to the International Monetary Fund's report published in April 2021, Turkey ranks at one of the bottom among the world countries in terms of pandemic expenditure, with 1.5 percent of the Gross Domestic Product. The economic difficulties experienced by individuals who have very few employment opportunities due to COVID-19 and who cannot access adequate social and economic assistance may affect the treatment of chronic metabolic diseases and can cause irreversible problems in the lives of these individuals. Ensuring adequate economic support for these individuals and their families is of great importance to prevent permanent damage that may occur.

Limitations

Our study has a number of limitations. The COVID-19 traumatic stress scale was applied to patients and their relatives, and there were no control groups in our study. The identification of COVID-19-related problems that individuals with LSD specifically experience can be investigated further by including control groups. Although a significant number of the patients followed in our unit have been reached, the small sample size is another limitation of our study.

Conclusion

The pandemic brought wide-ranging changes in the treatment

and follow-up of patients with rare diseases. The most effective way to maintain access to treatment during a pandemic appears to be home therapy; however, the personnel involved should be monitored and much attention should be paid to the proper use of personal protective equipment. When home therapy is not possible, safe infusion centers should be established in hospitals, which separates patients with COVID-19 and non-COVID-19. Ensuring the safe transfer of patients to health centers can also be helpful. It is also of great importance to provide adequate social and economic support to individuals who are economically disadvantaged. In order to reduce the negative health effects caused by the interruption of treatment, psychological support is of great importance.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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